

## INTERNET COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

Date of mailing (day/month/year) 03 January 2001 (03.01.01)	
International application No. PCT/GB00/01520	Applicant's or agent's file reference KR/P32292
International filing date (day/month/year) 19 April 2000 (19.04.00)	Priority date (day/month/year) 23 April 1999 (23.04.99)
Applicant BLACKLER, Paul, David, James et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

21 November 2000 (21.11.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. Mafla Telephone No.: (41-22) 338.83.38
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## CORRECTED VERSION

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
2 November 2000 (02.11.2000)

PCT

(10) International Publication Number  
**WO 00/64896 A1**

(51) International Patent Classification<sup>7</sup>: C07D 417/12,  
A61K 31/44, A61P 3/10

Beecham (Cork) Limited, Curraghbinny, Carrigaline,  
County Cork (IE).

(21) International Application Number: PCT/GB00/01520

(74) Agent: RUTTER, Keith; SmithKline Beecham, Two New  
Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(22) International Filing Date: 19 April 2000 (19.04.2000)

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BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK,  
DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID,  
IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,  
LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL,  
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KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent  
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(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,  
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GW, ML, MR, NE, SN, TD, TG).

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25 October 2001

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see PCT Gazette No. 43/2001 of 25 October 2001, Section  
II

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: POLYMORPH OF 5-[4-[2- (N-METHYL-N-( 2-PYRIDYL)AMINO) ETHOXY]BENZYL] THIAZOLI-  
DINE-2,4-DIONE, MALEIC ACID SALT

(57) Abstract: A polymorphic form of 5-[4-[2- (N-methyl-N-( 2-pyridyl)amino) ethoxy]benzyl] thiazolidine-2, 4-dione, maleic acid salt (the "Polymorph") characterised in that it provides: (i) an infra red spectrum containing peaks at 1763, 912, 856 and 709 cm<sup>-1</sup>; and/or (ii) a Raman spectrum containing peaks at 1762, 1284, 912 and 888 cm<sup>-1</sup>; and/or (iii) a solid-state <sup>13</sup>C nuclear magnetic resonance spectrum containing peaks at 111.0, 113.6, 119.8, 129.1, 130.9, 131.8, 134.7, 138.7, 146.5, 152.7, 157.5, 169.5, 171.0, 178.7 ppm; and/or (iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 5.87, 5.30, 4.69, 4.09, 3.88, 3.61, 3.53 and 3.46 Angstroms; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

WO 00/64896 A1



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : C07D 417/12, A61K 31/44, A61P 3/10		A1	(11) International Publication Number: WO 00/64896
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(21) International Application Number: PCT/GB00/01520 (22) International Filing Date: 19 April 2000 (19.04.00) (30) Priority Data: 9909473.2 23 April 1999 (23.04.99) GB 9912196.4 25 May 1999 (25.05.99) GB (71) Applicants (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). SMITHKLINE BEECHAM (CORK) LIMITED [IE/IE]; Curraghbinny, Carrigaline, County Cork (IE). (72) Inventors; and (75) Inventors/Applicants (for US only): BLACKLER, Paul, David, James [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). BROWNE, Christine, Marie [IE/IE]; SmithKline Beecham (Cork) Limited, Curraghbinny, Carrigaline, County Cork (IE). COAKLEY, Timothy, G. [IE/IE]; SmithKline Beecham (Cork) Limited, Curraghbinny, Carrigaline, County Cork (IE). GILES, Robert, Gordon [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). MORRISSEY, Gillian [IE/IE]; SmithKline Beecham	(Cork) Limited, Curraghbinny, Carrigaline, County Cork (IE). (74) Agent: RUTTER, Keith; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report.
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(54) Title: POLYMORPH OF 5-[4-[2- (N-METHYL-N-( 2-PYRIDYL)AMINO) ETHOXY]BENZYL] THIAZOLIDINE-2,4-DIONE, MALEIC ACID SALT

(57) Abstract.

A polymorphic form of 5-[4-[2- (N-methyl-N-( 2-pyridyl)amino) ethoxy]benzyl] thiazolidine-2, 4-dione, maleic acid salt (the "Polymorph") characterised in that it provides: (i) an infra red spectrum containing peaks at 1763, 912, 856 and 709 cm<sup>-1</sup>; and/or (ii) a Raman spectrum containing peaks at 1762, 1284, 912 and 888 cm<sup>-1</sup>; and/or (iii) a solid-state <sup>13</sup>C nuclear magnetic resonance spectrum containing peaks at 111.0, 113.6, 119.8, 129.1, 130.9, 131.8, 134.7, 138.7, 146.5, 152.7, 157.5, 169.5, 171.0, 178.7 ppm; and/or (iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 5.87, 5.30, 4.69, 4.09, 3.88, 3.61, 3.53 and 3.46 Angstroms; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

# INTERNATIONAL SEARCH REPORT

Intern: Application No  
PCT/00/01520

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D417/12 A61K31/44 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 99 31093 A (SMITHKLINE BEECHAM PLC) 24 June 1999 (1999-06-24) cited in the application claims 1-17 page 6; example 1 ---	1-14
A	WO 98 55122 A (SMITHKLINE BEECHAM PLC ET AL) 10 December 1998 (1998-12-10) claims 1-21 page 2, line 22 -page 3, line 13 ---	1-14
A	WO 94 05659 A (SMITHKLINE BEECHAM PLC) 17 March 1994 (1994-03-17) cited in the application claims 1-13 --- -/--	1-14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

5 July 2000

Date of mailing of the international search report

14/07/2000

Name and mailing address of the ISA  
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Authorized officer

Siatou, E

# INTERNATIONAL SEARCH REPORT

International Application No

PC 00/01520

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HALEBLIAN J ET AL: "PHARMACEUTICAL APPLICATIONS OF POLYMORPHISM" JOURNAL OF PHARMACEUTICAL SCIENCES, US, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, vol. 58, no. 8, 1 August 1969 (1969-08-01), pages 911-929, XP002020518  ISSN: 0022-3549  page 913, right-hand column, last paragraph -page 914, left-hand column, line 5</p> <p style="text-align: center;">-----</p>	1-14

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT 00/01520

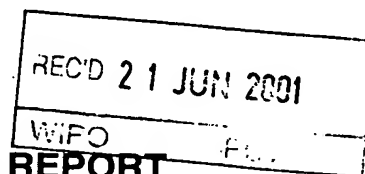
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9931093 A	24-06-1999	AU 2272299 A	05-07-1999
WO 9855122 A	10-12-1998	AU 8215098 A	21-12-1998
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WO 9405659 A	17-03-1994	AT 182147 T	15-07-1999
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		SK 27795 A	09-08-1995
		US 5741803 A	21-04-1998
		US 5910592 A	08-06-1999
		ZA 9306509 A	16-06-1994

# ATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference SD/KP/P32292	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01520	International filing date (day/month/year) 19/04/2000	Priority date (day/month/year) 23/04/1999
International Patent Classification (IPC) or national classification and IPC C07D417/12		
Applicant SMITHKLINE BEECHAM PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  21/11/2000	Date of completion of this report  19.06.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Fritz, M  Telephone No. +49 89 2399 2792  



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01520

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

### Description, pages:

1-10 as originally filed

### Claims, No.:

1-14 as originally filed

### Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01520

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 14.

because:

☒ the said international application, or the said claims Nos. with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

### V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims 1-13

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01520

	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

- D1: WO 94 05659 A (SMITHKLINE BEECHAM PLC) 17 March 1994 (1994-03-17)  
cited in the application
- D2: HALEBLIAN J ET AL: 'PHARMACEUTICAL APPLICATIONS OF  
POLYMORPHISM' JOURNAL OF PHARMACEUTICAL  
SCIENCES,US,AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON,  
vol. 58, no. 8, 1 August 1969 (1969-08-01), pages 911-929, XP002020518 ISSN:  
0022-3549

The present application relates to a special crystalline form of the maleic acid salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (claims 1-8), a process for preparing this compound (claim 9), a pharmaceutical composition thereof (claim 10), the compound according to claim 1 for use as a therapeutically active substance (claim 11) and for use in the treatment and/or prophylaxis of diabetes mellitus (claim 12), the usage thereof for the manufacture of a medicament (claim 13) as well as a method of treatment by administering the compound according to claim 1 (claim 14)

For the assessment of the present claim 14 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not

recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Example 1 of D1 describes a crystalline form of the maleate salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione which was characterized by  $^1\text{H}$  NMR spectroscopy. It is stated in the present application that the compound described herein represents a different crystalline form of this known compound. There are no  $^1\text{H}$  NMR data given in the present application, the different preparation procedures in the prior art and the present application make it however plausible that the maleate salt described in the present case is indeed a different crystalline form.

In D1 (p. 1, lines 24-25) it is emphasized that the salts of the compounds I (of which 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione is a representative) are characterized by significant formulation and bulk handling advantages.

D2 generally relates to polymorphism of pharmaceutically useful substances.

Therefore the subject-matter of claims 1-13 according to the present case is deemed to be novel in the sense of Article 33(2) PCT.

The problem of the present application was to provide 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione in a form which is particularly suitable for bulk preparation and handling.

Closest prior art is D1.

D1 emphasizes the significant formulation and bulk handling advantages of pharmaceutically acceptable salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (which was demonstrated in ex. 1 and also ex. 2 of D1). Polymorphism of pharmaceutically useful substances is a phenomenon which is well known in the art.

To solve the problem underlying the present case a person skilled in the art simply had to vary the preparation procedure described in examples 1 and 2 of D1 in order to ar-

rive at a different crystalline modification of this known compound.

As it is already known from D1 that salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione show formulation and bulk handling properties which are superior to those of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione itself and polymorphism of this kind of substances is also known in the art (vide supra), an inventive activity was not necessary to solve the problem underlying the present case.

As the applicant has not demonstrated an unexpected effect which distinguishes the crystalline form of the maleate salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]-benzyl]thiazolidine-2,4-dione according to the present case further from the crystalline compound described in ex. 1 of D1, an inventive step in the sense of Article 33(3) PCT is not acknowledged for the subject-matter of claims 1-13.

#### **Re Item VIII**

##### **Certain observations on the international application**

Obviously claim 13 refers to the compound according to claim 1. This should be indicated in order to fulfill the requirements set forth in Article 6 PCT.